

## Review Article

# Screening for Thyroid Dysfunction in Pregnancy: Is It Worthwhile?

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There is a high incidence of thyroid dysfunction during pregnancy resulting in adverse maternal (miscarriages, anaemia in pregnancy, preeclampsia, abruptio placenta and post-partum haemorrhage) and fetal effects (premature birth, low birth weight, increased neonatal respiratory distress) which may justify screening for thyroid function during early pregnancy with interventional levothyroxine therapy for thyroid hypofunction. There is a greater prevalence of subclinical hypothyroidism in women with delivery before 32 weeks and there is even an association between thyroid autoimmunity and adverse obstetric outcome, which is independent of thyroid function. Higher maternal TSH levels even within the normal reference range are associated with an increased risk of miscarriages, fetal and neonatal distress and preterm delivery. There are few prospective randomised trials to substantiate the benefit of screening and the recently reported CATS study did not show a benefit in child IQ at age 3 years. Nevertheless there seems to be a case for screening to prevent adverse obstetric outcomes. The clinical epidemiological evidence base does not justify universal screening at the present time. However, it is probable that more evidence will be produced which may alter this view in the future.

## 1. Introduction

Thyroid disorders are common. The prevalence of hyperthyroidism is around 5 per 1000 in women and overt hypothyroidism about 3 per 1000 in women. Subclinical hypothyroidism has a prevalence in child bearing age women in iodine sufficient areas of between 4 and 8%. As the conditions are generally much more common in the female it is to be expected that they will appear during pregnancy. During the last decade there has been an increasing appreciation of the incidence of thyroid dysfunction during pregnancy as well as the resultant adverse maternal and fetal effects [1–3]. In the hope that many of these adverse effects could be prevented or ameliorated by early detection and appropriate treatment the proposal to implement screening for thyroid function during pregnancy deserves consideration.

## 2. Screening for Disease

Medical screening is the systematic application of a test or inquiry to identify individuals at sufficient risk of a specific

disorder to benefit from further investigation or direct preventive action [4]. The requirements for a justifiable screening test are shown in Table 1.

It will be apparent that screening a population must be considered very carefully in respect of the condition being screened for, the effectiveness (and safety) of any intervention, and the potential anxiety of the patient. If the effectiveness is not known with certainty then evidence should be sought, usually in the form of a randomised trial.

## 3. Does Thyroid Screening in Pregnancy Meet the Above Criteria for Screening?

The prevalence of Graves' disease is approximately 3.0/1000 with an incidence of about 0.5/1000/year. The prevalence and incidence in women during child bearing years is not known but thyrotoxicosis is said to occur in 2/1000 pregnancies and Graves' disease would be expected to account for at least 80% of these cases. While these figures are low, Graves' hyperthyroidism can have a dramatic effect on the mother

TABLE 1: Justification for screening test (adapted from Wald and Law 2010 [4]).

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- (1) Well-defined disorder with known incidence/prevalence.
  - (2) Medically important disorder.
  - (3) Screening test simple and safe with established cutoff values.
  - (4) Effective treatment available.
  - (5) Cost of test relative to benefit should be known.
  - (6) Adequate logistics for the testing and followup.
  - (7) Patient and management acceptability.
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as well as the fetus. There are significant maternal complications including miscarriage, placenta abruptio, preterm delivery, and pre-eclampsia [5]. One to 5% of neonates of mothers with Graves' disease have hyperthyroidism due to the transplacental passage of maternal stimulating thyrotropin receptor antibodies (TRAbs) [6]. This may occur even though the mother may be euthyroid and has received previous treatment for Graves' disease. Neonatal hyperthyroidism may also be due to an activating mutation of the TSH receptor dominantly inherited from the mother. Transient neonatal central hypothyroidism is due to poorly controlled Graves' disease leading to suppression of the fetal pituitary thyroid axis due to placental transfer of T4 [7]. Subclinical hyperthyroidism (i.e., normal circulating concentrations of T4 and T3 but subnormal TSH levels) occurs in approximately 1.7% of pregnant women and is not associated with adverse pregnancy outcomes [8]. Screening for this condition is clearly not warranted, although if a low TSH is found the establishment of the cause will improve obstetric outcome in a number of women [9].

In contrast to hyperthyroidism, hypothyroidism is quite common in pregnancy [10]. The incidence of subclinical hypothyroidism (raised TSH and normal or low normal T4) is at least 2.5%, and these women have no clinical features and are often asymptomatic, but 50–60% will have evidence of autoimmune thyroid disease (positive TPOAbs and or thyroglobulin antibodies, TgAbs) in iodine-sufficient areas. It should be noted however that endemic iodine deficiency is the most common cause of hypothyroidism seen in pregnant women worldwide. Overt hypothyroidism occurs in only about 5% of all women who have a high TSH. During the last decade, it has become apparent that untreated maternal hypothyroidism and subclinical hypothyroidism in pregnancy is associated with adverse fetal and obstetric outcomes [11, 12]. These events include miscarriages, anaemia in pregnancy, preeclampsia, abruptio placenta, and postpartum haemorrhage while premature birth, low birth weight, increased neonatal respiratory distress, and more admissions to the neonatal intensive care unit have been described in babies born to mothers with hypothyroidism [13]. There is a greater prevalence of subclinical hypothyroidism in women with delivery before 32 weeks, and there is even an association between thyroid autoimmunity and adverse obstetric outcome, which is independent of thyroid function [14]. Higher maternal TSH levels even within the normal reference range are associated with an increased risk of miscarriages, fetal and neonatal distress [15] as well as preterm delivery [16]. In a prospective study, euthyroid

TPOAb+ve women who received interventional L-thyroxine in early pregnancy had a reduced miscarriage rate and less preterm delivery [17]. Further prospective randomised trials are required to confirm these interesting data. Of equal or even greater importance than the above is the detrimental effect of hypothyroidism during pregnancy on fetal brain development. The availability of thyroxine to the developing fetal neurones is vital for their maturation and proper function [18]. Two studies [19, 20] have shown that low thyroid hormone concentrations in early gestation can be associated with significant decrements of IQ of the children when tested at 7 years and 10 months, respectively. Pop et al. [21] have also shown a significant decrement in IQ in children aged 5 years whose mothers were known to have circulating anti-TPO antibodies at 32-week gestation and were biochemically euthyroid. Moreover, as shown by Haddow et al. [22], the 7-year-old children of women known to be hypothyroid during gestation showed impaired psychological development compared to children of the same age from carefully matched control mothers whose thyroid function was known to be normal during pregnancy. In this paper it is interesting that a subgroup of children whose mothers had been receiving thyroxine for hypothyroidism during pregnancy (albeit at inadequate doses as evidenced by high TSH during pregnancy) also showed some impairment of psychological performance although not as great as the other children. The neurodevelopmental impairment is similar to that seen in iodine-deficient areas and implies that iodine status should be normalised in regions of deficiency. However, much of the USA and parts of Europe are not iodine deficient which raises the question of routine screening of thyroid function during early pregnancy or even at preconception. It is now appreciated that similar decrements in mentation can be seen in iodine-deficient areas as well as iodine-sufficient ones thus providing further evidence for the role of thyroid hormone in fetal neurodevelopment.

Isolated hypothyroxinaemia (low FT4 and normal TSH) either due to iodine deficiency or autoimmune thyroid disease has been shown to result in lower IQ in infants and young children in retrospective [22] and prospective [23] studies. Although it has been found not to be associated with adverse perinatal outcomes [24], it is associated with reduced motor and intelligence performance in neonates [25] and in children aged 25–30 months in a Chinese population [26]. While treatment of overt hypothyroidism has been shown to prevent the obstetric and neonatal complications the evidence for treatment of subclinical hypothyroidism in prevention is less secure. However, in a recent screening study where women were characterised as high risk or low risk in terms of the chance of adverse obstetric outcome there was a significant reduction in these outcomes even in low-risk women who were screened for subclinical hypothyroidism [27].

#### 4. Evidence for Intervention in High-Risk Clinical Situations

The strength of evidence relating maternal hypothyroidism to low IQ in children suggests strongly that screening thyroid

function in early gestation with l-thyroxine intervention in appropriate women would be beneficial. In addition there is evidence that such a strategy would be cost-effective. A study by Thung et al. [28] compared the cost-effectiveness of no screening versus routine screening for subclinical hypothyroidism in pregnancy. The decision model demonstrated a saving of approximately \$8.3 million per 100,000 women screened with an increment of 589.3 quality adjusted life years. Similar results were obtained by Dosiu et al. [29] using a different screening model.

Several organisations have issued guidelines on whether to adopt a screening strategy for thyroid function in early pregnancy [30–32]. The most recent published recommendations are from the Endocrine Society of America [33] which do not endorse universal screening. Instead, a targeted approach is suggested in which screening would be offered to women with a family history of thyroid or other autoimmune disease as well as to women with any risk factors for thyroid dysfunction (e.g., previous neck irradiation, previous thyroid surgery). Although this would seem a reasonable approach in relation to economic and logistic factors there has been accruing evidence that a substantial number of women with thyroid dysfunction would not be diagnosed in these circumstances. Vaidya [34] found that targeted testing of a previously defined high-risk group who had a personal history of thyroid or other autoimmune disorders or a family history of thyroid disease (413 women) failed to detect 28% of pregnant women with a TSH > 4.2 mIU/L. Li et al. [26] found that this strategy missed 36% of women with TSH > 4.0 mIU/L. In the study of Negro et al. [27], screening “low-risk women” identified 28% with thyroid dysfunction excluding those with just positive thyroid antibodies. The variability seen in these data may relate to different definitions of thyroid dysfunction and different ethnicity of the populations studied. Further work in this area is required. At the time of writing this paper the unpublished guidelines from The American Thyroid Association did not recommend screening while members from the as yet unpublished guidelines from The American Endocrine Society guidelines committee were divided 50/50 as to their recommendations.

At present there are no published prospective controlled trials of a screening strategy assessing child IQ. Preliminary results from a prospective randomized trial of L-T4 treatment in women screened prior to 16-week gestation (compared with control women not screened and therefore not treated with L-T4), the CATS study, are now available. The mean IQ of the two groups of children (screen and control) was not different. However, an on-treatment analysis showed that the number of children with IQ > 85 born to women with subclinical hypothyroidism who were considered to have been compliant with their T4 treatment was significantly less (9%) than that in the control group (15%).

## 5. Conclusion

The screening criteria for subclinical hypothyroidism in pregnancy are largely met. The condition is not rare, and several retrospective studies imply adverse obstetric and

child neurodevelopmental outcomes. However there are few prospective randomised trials to substantiate the benefit of screening, and the recently reported CATS study did not show a benefit in child IQ at age of 3 years. Nevertheless there seems to be a case for screening to prevent adverse obstetric outcomes. From the child cognitive function aspect there should be further studies where intervention is initiated early in the first trimester during the course of brain development. Results of such a study being conducted by the National Institutes of Health are awaited.

From the forgoing discussion this author believes that the clinical epidemiological evidence base does not justify universal screening at the present time. However, it is probable that more evidence will be produced which may alter this view in the future.

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